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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,936	01/23/2001	Nila Patil	20654-000200US	3843

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	15

DATE MAILED: 02/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/768,936	Patil
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 14, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 14, 2003 has been entered.

Specification

2. Claims 15-37 have been canceled without prejudice towards further prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-6 and 12-14 are rejected under 35 U.S.C. 103 (a) over Sicilliano et al. (U.S. Patent 5,538,869) (July 23, 1996) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001).

Sicilliano et al teach a method of analyzing a subset of nucleic acids within a nucleic acid population (Abstract and Examples 4-7):

a) providing a population of nucleic acid fragments at least some of which have sequences that are repeated more than once in a genome (Column 7, line 44 to column 8, line 26 and Example 4 and Figure 20 and Prophetic Example 12);

b) incubating single stranded forms of the population of nucleic acid fragments under annealing conditions, whereby single stranded forms of nucleic acid fragments having repeat sequences preferentially hybridize to each other relative to nucleic acid fragments lacking repeat sequences (Claims 1-16 and Examples 1-6 and Figure 20 and Prophetic Example 12) ;

c) separating single stranded forms of the population of nucleic acid fragments from annealed double stranded forms, the single stranded forms being enriched for nucleic acid fragments lacking repeat sequence (Column 14, line 37 to column 15, line 14);

d) inherently hybridizing the separate single stranded forms of the population of nucleic acid fragments to a nucleic acid probe array and inherently teaches that annealed double-stranded

forms being enriched for nucleic acid fragments containing repeat sequences (metaphase spreads are considered as nucleic acid probe array as taught in Column 14, line 37 to column 15, line 14) ;

e) determining hybridization of the probes to the single stranded forms of the population of nucleic acid fragments, thereby analyzing the fragments (Figures 3-19 and Examples 8-10).

Sicilliano et al teach a method wherein the population of nucleic acid fragments span the chromosome of the human genomic fragments (Examples 4-8).

Sicilliano et al teach a method further comprising denaturing the population of nucleic acid fragments before the incubation step (Figure 20 and Prophetic Example 12).

Sicilliano et al teach a method wherein the determining indicates the presence of at least one variation in a fragment hybridized to the array relative to the reference sequence (Example 8 and Column 25, line 33 to column 28, line 25).

Sicilliano et al teach a method wherein the population of nucleic acid are from a chromosome from a first individual, and the reference sequence is that of a corresponding chromosome from a second individual (Column 25, line 33 to column 28, line 25).

Sicilliano et al do not teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained.

Cronin et al. teach an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic

acid from which the population of nucleic acid fragments was obtained (Abstract and Figures 1-9, and Example and Column 14, line 46 to Column 15, line 56).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the identification and banding of human chromosome of Sicilliano et al., since Cronin et al. state "An array of probes is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) (Column 14, lines 46-50." Cronin et al provides further motivation as Cronin et al. state, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences (Column 15, lines 30-33)". An ordinary practitioner would have been motivated to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the identification and banding of human chromosome of Sicilliano et al, in order to achieve the express advantages, as noted by Cronin et al., of an array of probes, which is most useful for analyzing the reference sequence from which the probes were designed

and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) and which also provides a particular advantage over conventional sequencing methods with its capacity of detecting and quantifying proportions of multiple target sequences simultaneously.

5. Claims 7-11 are rejected under 35 U.S.C. 103 (a) over Sicilliano et al. (U.S. Patent 5,538,869) (July 23, 1996) in view of Cronin et al. (U.S. Patent 6,309,823 B1) (October 30, 2001) further in view of Yamane et al. (U.S. Patent 5,601,976) (February 11, 1997).

Sicilliano et al in view of Cronin et al. teach the method of claims 1-6 and 12-14 as described above.

Sicilliano et al in view of Cronin et al. do not teach the separation of single stranded DNA from double stranded DNA by successively performing hydroxyapatite chromatography and HPLC.

Yamane et al. teach the separation of single stranded DNA from double stranded DNA by successively performing hydroxyapatite chromatography and HPLC (Column 23, lines 12-41).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the separation of single stranded DNA from double stranded DNA by successively performing hydroxyapatite chromatography and HPLC of Yamane et al. into the identification and banding of human chromosome of Sicilliano et al. in view of Cronin et al., since Yamane et al. state "Particularly octadecylsilane has been frequently utilized for high performance liquid chromatography, and can separate substances through differences in

hydrophilic property or hydrophobic property. Whereas, when considered on nucleic acids, double-stranded DNA is more hydrophilic than single-stranded DNA, because bases are mutually hydrogen bonded, stacking occurs between the bases and further the phosphoric diester is located outside of the double strand. Therefore, by the use of the above silica gel derivative, for example octadecylsilane, etc., single-stranded DNA can be easily separated from double-stranded DNA, wherein double-stranded DNA can be eluted first (Column 23, lines 29-41)." An ordinary practitioner would have been motivated to substitute and combine the separation of single stranded DNA from double stranded DNA by successively performing hydroxyapatite chromatography and HPLC of Yamane et al. into the identification and banding of human chromosome of Sicilliano et al. in view of Cronin et al. in order to achieve the express advantages, as noted by Yamane et al., of a purification step by which single-stranded DNA can be easily separated from double-stranded DNA.

Response to Arguments

6. Applicant's arguments filed on November 14, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant also argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Cronin et al as Cronin et al states, "A particular advantage of the present sequencing strategy over conventional sequencing methods is the capacity simultaneously to detect and quantify proportions of multiple target sequences (Column 15, lines 30-33)". An ordinary practitioner would have been motivated to substitute and combine an array, which comprises a set of probes complementary to a known reference sequence, the reference sequence being the same or variant of the sequence of a nucleic acid from which the population of nucleic acid fragments was obtained of Cronin et al. into the identification and banding of human chromosome of Sicilliano et al, in order to achieve the express advantages, as noted by Cronin et al., of an array of probes, which is most useful for analyzing the reference sequence from which the probes were designed and variants of that sequence exhibiting substantial sequence similarity with the reference sequence (e.g., several single base mutations spaced over the reference sequence) and which also provides a particular advantage over conventional sequencing methods with its capacity of detecting and quantifying proportions of multiple target sequences simultaneously.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., no repeat sequence-rich DNA is added to the nucleic acid fragments that are to be enriched for non-repeat containing DNA) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re*

Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The use of "comprising" language in the claims permits any additional step(s) or material(s) can be included in the claims. When Siciliano adds the two populations of DNA (one having repeat sequence and the other lacking repeat sequence) together, these two steps contribute to a process step as required by step© of claim 1.

Applicant then argues that the 103 rejection is improper because it lacks a reasonable expectation of success. This argument is not persuasive. There is evidence in the Sicilliano reference of the enabling methodology, and the suggestion to modify the prior art. Applicant argued that according to Siciliano's method, there will be no probe left for hybridization to the chromosome spread. This argument is not persuasive. Siciliano clearly states, "Remaining biotinylated probe (containing only chromosome-specific sequences) will then be directly hybridized to metaphase spreads to detect the specific human chromosome regions of interest" (Column 15, lines 5-8).

Applicant argues that Sicilliano reference does not teach the separating of single stranded forms of the population of nucleic acid fragments from annealed double stranded forms of the claimed invention. Applicant argues that the word "separating of single stranded DNA" was not found in Sicilliano reference. Applicant argues that because Sicilliano has a preferred embodiment of identification and banding of specific human chromosomes and regions, Sicilliano is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure

or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Sicilliano has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Sicilliano reference uses identification and banding of specific human chromosomes and regions, the property of "separating of single stranded DNA" is inherently present in this chemically and structurally identical molecule. For example, Sicilliano teaches the removal of repeat sequences (Column 14, line 37 to Column 15, line 14). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any repeat sequences can be considered as single stranded forms of the population of nucleic acid fragments.

Therefore, 103(a) rejections based on Sicilliano et al. in view of Cronin et al. is hereby properly maintained.

Applicant's arguments to withdraw 103(a) rejection based on Arnold et al reference is persuasive and therefore withdrawn accordingly. However, a new 103(a) rejection has been included. Applicant's arguments are moot in view of the new ground of rejection.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

January 24, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER